Manuscript rights

HOANG THI LIEN

SYNTHESIS AND STRUCTURE OF NOVEL *BIS*-THIOETHERS, SULFUR−CONTAINING HETEROCYCLES AND THIAMACROCYCLIC COMPOUNDS BASED ON 3,4-DIHALOGENO-FURAN-2(5*H*)-ONES AND DITHIOLS

02.00.03 – Organic chemistry

ABSTRACT

Of the thesis submitted for a degree of Doctor of Philosophy in Chemistry

Kazan – 2016

The research was performed in the Department of Organic Chemistry of A.M. Butlerov Institute of Chemistry of Federal State Autonomous Educational Institution of Higher Training «Kazan (Volga Region) Federal University».

Supervisor:	**Kurbangalieva Almira Rafaelovna** PhD, Associate Professor
Official opponents:	**Semenov Vyacheslav Engelsovich** Doctor of Chemical Sciences, Associate Professor, Head of the laboratory of chemistry of nucleotide bases of Federal State Government-financed Institution of Sciences «A.E. Arbuzov Institute of Organic and Physical Chemistry» Kazan Scientific Centre Russian Academy of Sciences
	Startseva Valeria Andreevna PhD, Associate Professor of Department of General and Organic Chemistry of State Government-financed Educational Institution of Higher Professional Training «Kazan State Medical University»
External reviewer:	Federal State Government-financed Educational Institution of Higher Training «N.G. Chernyshevsky Saratov National Research State University»

At 10 a.m. on June 30th 2016, the thesis defense will be held in the meeting of Dissertation Counsil D 212.081.30 on chemical sciences of FSAEI HT «Kazan (Volga Region) Federal University» by the address: Butlerov hall, A.M. Butlerov Institute of Chemistry, 18 Kremlyovskaya street, Kazan, 420008, Russia Federation.

The thesis can be found in N.I. Lobachevsky science library of FSAEI HT «Kazan (Volga Region) Federal University», http://www.kpfu.ru.

All reviews on the abstract in duplicate please send to Attestation department of scientific and pedagogical staff of KFU, 18 Kremlyovskaya street, Kazan, 420008, Russia Federation.

Abstract was sent on May 5th 2016.

Scientific secretary of
Dissertation council D 212.081.30,
PhD  Yakimova Ludmila Sergeevna

GENERAL CHARACTERISTIC OF THE RESEARCH

Motivation for the study. Today the chemistry of heterocyclic compounds has intensively developed due to a huge amount of possibilities of their use not only in chemical practise but also in biology, medicine, agriculture and different industries. The chemistry of of 2(5*H*)-furanones has recently attracted much attention. Many representatives of this class of five-member oxygen containing heterocycles exhibit a wide range of practically useful properties. They are demanded in organic synthesis. The 2(5*H*)-furanone fragment is present in a wide variety of natural and synthetic biologically active compounds. Substances having inflammatory, antibacterical, antifungal, antitumor and other kinds of biological activity were found among unsaturated γ-lactone ring containing compounds. Owing to the commercially availability, the presence of different reaction centers, high and multiple reaction capacity 3,4-dihalogenated 2(5*H*)-furanones are very attractive as starting materials and intermediates in synthetic chemistry of various functionalized derivatives of 2 (5*H*)-furanone and new classes of heterocyclic compounds having biological importance, and other practically useful properties.

Recently, reactions of different derivatives of 2(5*H*)-furanone with *N*-, *O*-, C- and *P*-containing nucleophilic reagents have been studied. As for *S,S*-binucleophilic reagents, from which a synthetic novelty can be expected by the participating of both functional groups in the reactions, only ethane-1,2-diol was used previously. A systematic study of reactivity of 3,4-dihalogenated derivatives of 2(5*H*)-furanone towards various dithiols wasn't conducted. In the literature there is no information about sulfur-containing macrocyclic compounds created on the basis of derivatives of 2 (5*H*)-furanone, which are promising in terms of discovering new biological, complexation and extraction properties.

Aims of the research were the elaboration of methods for the synthesis of novel bis-thioethers, sulfur-containing heterocycles and thiamacrocyclic compounds on the basis of 3,4-dihalogeno-2(5*H*)-furanones and dithiols and the study of structure of novel sulfanyl derivatives of 2(5*H*)-furanones.

The following main problems were formulated and solved to achieve these goals:

- Development of methods for the synthesis of novel sulfur containing derivatives of different structure on the basis of 3,4-dihalogeno-2(5*H*)-furanones and *S,S*-binucleophilic reagents;
- Establishment of regioselective reactions of 3,4-dihalogeno-2(5*H*)-furanones, containing halogenalkoxy-substitute at the C^5-atom of γ-lactone ring, with thiols and dithiols under base catalysis;
- Comparative study of reactivity of 5-hydroxy- and 5-alkoxy-3,4-dichloro-2(5*H*)-furanones towards various dithiols;
- Development of approaches to synthesis of sulfur-containing macrocyclic compounds, containing fragment of 2(5*H*)-furanone;
- Study of crystallization features of diastereomeric mixtures of *bis*-thioethers and thiamacrocycles based on 5*H*)-furanon.

Original Contribution of obtained results:

- We firstly established that the reactions of 3,4-dihalogeno-2(5*H*)-furanones contacting halogenalkoxy-substitue at the atom C^5 with thiols and dithiols in the presence of trimethylamine occur highly regioselectively with the substitution of the halogen atom at the atom C^4 of γ-lactone ring;
- The approaches to synthesis of novel thiilation products of different structure (thioethers, thiols, *bis*-thioethers, sulfanyl bi- and tricyclic spiro- and fused compounds) based on 3,4-dihalogeno-2(5*H*)-furanones;

- Sulfur containing macrocyclic compounds of various constitution and structure bearing unsaturated γ-lactone fragment were firstly synthesized, isolated in the form of pure pure diastereomers and characterized by X-ray;
- In the presence of cesium carbonate in dimethylformamide crossover of 2(5*H*)-furanone based *bis*-thiothers was detected;
- Crystallization behaviour of diastereomeric mixtures of 1,2- and 1,3-phenylenedimethanethiols was studied. *bis*-thiothers. A very rare case of the formation of solid solution of diastereomers is observed for three compounds.

The theoretical and practical significance. Methods for synthesis of 3,4-digalogeno-2(5*H*)-furanone based sulfur containing compounds of different structure: thiols, thioethers, *bis*-thioethers, bi- and tricyclic spiro- and fused compounds, as wel as first representatives of oxa-thia macrocycles, bearing 2(5*H*)-furanone fragment were developed. These molecules are very attractive as building blocks in synthesis of practically useful substances. Bio-screening activity of obtained 2(5*H*)-furanones has shown that they inhibit the growth and biofilm formation of *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*. Thus they can be viewed as promising objects for further development of antibacterial drugs. Synthezied sulfur containing macrocyclic compounds are interesting in terms of complexation and extraction properties.

Methodological base and methods of investigation. Thiilation methods under acid and base catalysis (trimethylamine, aqueous potassium hydroxide solution, caesium carbonate), were used to synthesize novel sulfur containing 2(5*H*)-furanone derivatives. A wide range of classical methods in organic synthesis and isolation of target products was applied. Using preparative column chromatography, recrystallization in some cases complex reaction mixtures were separated, not only major but also minor products were individualized and some pairs of configurational isomers were purely isolated. Structures of all newly synthesized heterocyclic compounds were proved by modern methods: IR spectroscopy, ^{1}H, ^{13}C {^{1}H} NMR, HSQC and high-resolution mass spectrometry. Molecular and crystal structures of 31 novel sulfanyl derivatives were characterized by single-crystal X-ray structure analysis.

Statements, taken out to the defense:

- Regioselective substitution of halogen atom at carbon atom C^4 of lactone ring in the reactions of tri- and tetrahalogen 2(5*H*)-furanone derivatives with 4-methylthiophenol, 2-mercaptoethanol-2, ethane-1,2-dithiol and propane-1,3-dithiol under base conditions;
- Approaches for synthesis of 2(5*H*)-furanone based *bis*-thioethers, in molecules of which two γ-lactone rings were connected by fragment of different dithiols;
- Crossover reactions of 2(5*H*)-furanone based *bis*-thioethers, leading to preparation of bi- and tricyclic fused *S*,*O*-heterocycles;
- Approaches for synthesis of sulfur containing thia-macrocyclic compounds of various structures bearing 2(5*H*)-furanone moiety;
- Formation of novel thiilation products of acyclic structures, thiols and spiro-cyclic componds in the reactions of 3,4-dihalogeno-2(5*H*)-furanones with dithiols under acid and base catalysis;
- Establishment of the structures of products of thiilation reactions of 3,4-dihalogeno-2(5*H*)-furanone based on the complex by comprehensive study using IR spectroscopy, ^{1}H, ^{13}C {^{1}H} NMR,chromatography-mass spectrometry and single-crystal X-ray structure analysis.

Degree of reliance on results. The degree of reliance on research results is proved by the use of complex of modern physical-chemical methods for structure establishment (spectroscopy IR, ^{1}H, ^{13}C NMR, HSQC, X-ray) and composition (elemental analysis, high-resolution mass-spectroscopy) of all novel synthesized compounds.

Approbation of resuls of the dissertation research. Main results of the dissertation research were presented and discussed at following conferences: IIIth International scientific conference "New directions in chemistry of heterocyclic compounds" (Pyatigorsk, 2013), IIIth All-Russian scientific conference (with international participation) "Synthesis and complexation successes" (Moscow, 2014), Uran scientific forum "Contemporary problems of organic chemistry" (Ekaterinburg, 2014), All-Russian school-conference of students, PhD students and young scientists "Materials and technologies of the XXI century" (Kazan, 2014), All-Russian youth scientific school-conference "Actual problems of organic chemistry" (Sheregesh town, Kemerovskya region, 2015), International congress of heterocyclic chemistry «COST–2015» (Moscow, 2015), IVth All-Russian conference on organic chemistry (Moscow, 2015).

Publications. Results of the dessertation were published in 4 articles in peer-reviewed scientific journals of BAK and 9 thesises in the materials of international and an all-Russian conferences.

Author's contributuion is as follows: literature screening and analyzing thiilation reactions of 2(5*H*)-furanone derivatives and methods for preparation of thia-macrocyclic compounds, which were generalized in the literature review, planning and carrying out experiments, analyzing datas of spectral methods for establishment structure of novel synthesized compounds, as well as genelizing obtained results. All results included in the dissertation were obtained personally by author or with her direct participation. Single-crystal X-ray structure analysis X-ray was performed by PhD, researcher A.E Butlerov IOPC KSC AS O.A. Lodochnikova. Biological researches were taken by scientific group of PhD, Associate Professor of Department of Genetics of Institute of Fundamental Medicine and Biolology of KFU A.R. Kayumov.

The size and structure of the research. The dissertation is stated on 159 pages of the typewritten text, containing 28 schemes, 22 figures and 1 table. The research consists of the introduction, three chapters, the main results and conclusions, refrence list of 181 names and one Annex.

The literature review on reactivity of different 2(5*H*)-furanone derivatives toward oxygen-, sulfur-containing mono- and binucleophilic reagents, as well as general methods for preperation of thia-macrocyclic compounds is presented in the fist chapter. In the second one results our studies on reactions of 3,4-dihalogeno-2(5*H*)-furanones with various dithiols under acid and base conditions and methods for the synthesis of sulfur-containing macroheterocyclic compounds bearing 2(5*H*)-furanone fragment were shown. Experimental part including a description of the syntheses and spectral studies was given in the third charpter.

Author expresses her sincere gratitude to supervisor – Kurbangalieva Almira Rafaelievna for the support and great help in the writing of the thesis, to Chmutova Galina Alekseevna for her understanding, support and aid in the preparation for the PhD's exam in organic chemistry, Berdnikov E.A. for valuable advices on NMR spectra interpretation, Lodochnikova Olga Aleksandrovna for performance of X-ray diffraction analysis of synthesized compounds, Latypova Lilia Zinyrovna for NMR spectra registration, students Khaziev Rail Maratovich, Kuzmichova Margarita Jurevna and Zaripova Aigul Ramilievna for active assistance. Author also expresses her special thanks to Government of the

Socialist Republic of Vietnam for scholarships and an opportunity to study at Kazan Federal University

MAIN RESULTS AND CONCLUSIONS:

1. 60 novel substances of various structures based on 3,4-dihalogeno-2(5*H*)-furanones: ethers, thioethers, thiols, *bis*-thioethers, bi- and tricyclic spiro- and fused compounds, as well as first representatives of oxa-thia-macrocycles, containing 2(5*H*)-furanone fragment were synthesized.

2. High regioselective substitution of halogen atom at unsaturated carbon atom C^4 of lactone ring in reactions of 3,4-dihalogeno-2(5*H*)-furanones containing halogenalkoxy-substitute at carbon atom C^5 with 4-methylthiophenol, 2-mercaptoethanol and dithiols in the presence of trimethylamine was observed.

3. Thiilation reactions of 3,4-dihalogeno-2(5*H*)-furanones with different dithiols (ethane-1,2-dithiol, propane-1,3-dithiol, 1,2- and 1,3-phenylenedimethanethiol) under acid and base conditions occur advantageously with the formation of *bis*-thioethers, in molecules of which two γ-lactone rings connected by the fragment of dithiols at the carbon atoms C^4 and C^5 of five-membered cycle. By interaction of 5-metoxy- and 5-metoxy-3,4-dichloro-2(5*H*)-furanones with 2,2'-oxydiethanethiol in the presence of trimethylamine besides *bis*-thioethers products of 4-monothiosubstitution with a free thiol group in the side chain were formed.

4. It's been shown that, S–C^4 bond breaking and crossover of molecules of 2(5*H*)-furanone *bis*-thioethers in high dilution conditions in DMF in the presence of caesium carbonate and dithiols take place with the formation of new sulfur-containing bi- and tricyclic fused heterocycles containing 2(5*H*)-furanone fragment.

5. Approaches to synthesis of novel sulfur-containing 1+1 macrocyclic compounds, bearing 2(5*H*)-furanone moiety were developed. The method based on the reactions of 5,5'-(ethane-1,2-dioxy)*bis*(3,4-dichloro-2(5*H*)-furanone) with dithiols in high dilution conditions in DMF in the presence of caesium carbonate. 2+2 Oxa-thia-macrocyclic compounds were obtained by interacting of *bis*-ether with 1,2-phenylenedimethane and 2,2'-oxydiethanethiol in acetone in the presence of trimethylamine. In aqueous potassium hydroxide solution a novel *S,O*-macrocyclic compound containing 18 membered oxa-thia-macrocyclic and two 2(5*H*)-furanone moieties was synthesized in the result of a substitution of the chlorine atom at the carbon atom C^3 of thiols bearing 2(5*H*)-furanone.

6. According to X-ray analysis three *bis*-thioethers based on *o*-phenylenedimethanethiol with hydroxyl- and metoxy-groups at the fifth position of lactone ring crystallized as a solid solution of diastereomers. In the case of *bis*-thioethers with a few bigger substitute (OC_2H_5, OCH_2CH_2Cl), as well as some *bis*-thioethers based on other thiols diastereomers crystallized as separate entities or "conglomerate-like" behavior.

The main content of the dissertation was set out in following publications:

1. Kayumov, A. R. Inhibition of biofilm formation in *Bacillus subtilis* by new halogenated furanones / A. R. Kayumov, E. N. Khakimullina, I. S. Sharafutdinov, E. Y. Trizna, L. Z. Latypova, L. T. Hoang, A. B. Margulis, M. I. Bogachev, A. R. Kurbangalieva // The Journal of Antibiotics. – 2015. – V. 68. – № 5. – P. 297–301.

2. Hoang, L. T. *Bis*-thioethers based on 3,4-dichloro-2(5*H*)-furanones and propane-1,3-dithiol / L. T. Hoang, A. R. Kurbangalieva, A. S. Ezhrova, E. A. Berdnikov, G. A. Chmutova // Butlerov Communications. – 2015. – V. 42. – № 4. – P. 33–40.
3. Hoang, L. T. About novel products of mucochloric acid with 1,2-ethanedithiol under basic conditions / L. T. Hoang, A. R. Kurbangalieva, A. S. Ezhrova, O. A. Lodochnikova, G. A. Chmutova // Butlerov Communications. – 2016. – V. 45. – № 2. – P. 52–58.
4. Kurbangalieva, A. R. First example of the synthesis of *S*,*O*-macroheterocycle based on 2(5*H*)-furanone and 2,2'-oxydiethanethiol / A. R. Kurbangalieva, L. T. Hoang, O. A. Lodochnikova, M. J. Kuzmichova, A. R. Pradipta, K. Tanaka, G. A. Chmutova // Russ. Chem. But. − 2016. − № 5. − P. 1278–1284.
5. Hoang, L. T. The synthesis of 2(5*H*)-furanone *bis*-thioethers and their reactions with dithiols / L. T. Hoang, R. M. Khaziev, O. A. Lodochnikova, E. A. Berdnikov, A. R. Kurbangalieva // New directions in chemistry of heterocyclic compounds: Abstracts of IIIth International scientific conference (Pyatigorsk, 17–21 September 2013). – 2013.– P. 219.
6. Hoang, L. T. The interaction of 3,4-dichloro-2(5*H*)-furanones with sulfur-containing binucleophilic reagents // L. T. Hoang, R. M. Khaziev, A. R. Zaripov, A. R. Kurbangalieva, G. A. Chmutova // Synthesis and complexation successes: Abstracts of IIIth All-Russian scientific conference (with international participation), (Moscow, 21–25 April 2014). – 2014. – P. 205.
7. Hoang, L. T. 2(5*H*)-furanone *Bis*-thioethers in the synthesis of novel sulfur-containing heterocycles / L. T. Hoang, R. M. Khaziev, A. R. Zaripova, O. A. Lodochnikova, A. R. Kurbangalieva // Contemporary problems of organic chemistry: Abstracts of XVIIth school-conference of young scientists on chemistry in Uran scientific forum (Ekaterinburg, 8–12 June 2014). – 2014. – P. 87.
8. Zaripova, A. R. Synthesis and crystallization of the products of the reactions of 3,4-dichloro-2(5*H*)-furanones with phenylenedimethanethiols / A. R. Zaripova, L. T. Hoang, O. A. Lodochnikova, E. A. Berdnikov, G. A. Chmutova, A. R. Kurbangalieva // Materials and technologies of the XXI century: Abstracts of All-Russian school-conference of students, PhD students and young scientists (Kazan, 11–12 December 2014). – 2014 – P. 238.
9. Kuzmichova, M. J. Reactions of 3,4-dichloro-2(5*H*)-furanones with 2,2'-oxydiethanethiol / M. J. Kuzmichova, L. T. Hoang, O. A. Lodochnikova, G. A. Chmutova, A. R. Kurbangalieva // Materials and technologies of the XXI century: Abstracts of All-Russian school-conference of students, PhD students and young scientists (Kazan, 11–12 December 2014). – 2014 – P. 264.
10. Hoang, L. T. Sulfur-containing binucleophilic reagents in the synthesis of novel *S*-heterocycles and thia-macrocycles based on 2(5*H*)-furanone / L. T. Hoang, M. Kuzmichova, O. Lodochnikova, G. Chmutova, A. Kurbangalieva // Actual problems of organic chemistry – 2015: Abstracts of All-Russian youth scientific school-conference (Sheregesh town, Kemerovskya region, 21–27 March 2015). – 2015. – P. 86.
11. Hoang, L. T. Synthesis and different crystallization behaviors of diastereomeric mixtures of products of reactions of 3,4-dihalogeno-2(5*H*)-furanones with 1,2-phenylenedimethanethiol / L. T. Hoang, A. Zaripova, O. Lodochnikova, G. Chmutova, A. Kurbangalieva // Actual problems of organic chemistry – 2015: Abstracts of All-Russian youth scientific school-conference (Sheregesh town, Kemerovskya region, 21–27 March 2015). – 2015. – P. 184.
12. Kurbangalieva, A. R. Novel sulfur-containing heterocycles and thia-macrocycles based on 3,4-dichloro-2(5*H*)-furanones and dithiols / A. R. Kurbangalieva, L. T. Hoang, O. A. Lodochnikova, M. J. Kuzmichova, A. R. Zaripova, G. A. Chmutova // Book of abstracts of

the International congress on heterocyclic chemistry “COST–2015”. (Moscow, October 18–23, 2015). – 2015. – P. 151.
13. Kurbangalieva, A. R. Novel sulfur-containing heterocycles and thia-macrocycles based on 3,4-dichloro-2(5*H*)-furanones and dithiols / A. R. Kurbangalieva, L. T. Hoang, O. A. Lodochnikova, M. J. Kuzmichova, A. R. Zaripova, G. A. Chmutova // Book of abstracts of IVth All-Russian conference on organic chemistry. (Moscow, 22–27 November 2015). – 2015. – P. 49.